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OSTEOMYELITIS: PATHOGENESIS, CLINICAL AND THERAPEUTIC CHALLENGE

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ABSTRACT

Osteomyelitis refers to bone inflammation due to infection. Osteomyelitis is progressive infection (acute, sub-acute, and chronic to persistent) that results in inflammatory destruction, necrosis, and bone deformation secondary to pyogenic bacteria, mycobacteria and fungi. In children, the long bones are usually affected but in the adults, the vertebrae and the pelvis are most commonly involved. Many classification systems are available based on etiology, pathogenesis, and degree of bone involvement, duration, mechanism of infection, and presence of vascular insufficiency as well as age and the immune condition of the patient. Diabetic foot ulcers lead to bony infections resulting into high morbidity & mortality therefore, special attention is required.This paper reviews the microbiologic, clinical and non-surgical therapeutic considerations of osteomyelitis, with brief description of rare osteomyelitis of SAPHOsyndrome.

KEYWORDS: Osteomyelitis, *Staphylococcus Aureus*, Therapy

INTRODUCTION

Osteomyelitisis progressive infection that results in inflammatory destruction, necrosis, and bone deformation, which can progress to chronic and persistent stage (1). Most often caused by pyogenic bacteria, it may also be caused by mycobacteria and fungi (2). However, it is not a single; entity this disease is differentiated according to the etiology, pathogenesis, and degree of bone involvement, as well as age and the immune condition of the patient (3). It can involve different structure such as the bone marrow, cortex, periosteum, and parts of the surrounding tissues, or remain localized. Several classification schemes have been proposed. Waldvogel*et al* and Cierny-Mader are the most accepted (2, 4, 5). Waldvogel's system is based on duration, mechanism of infection, and presence of vascular insufficiency, providing the following classification: 1) acute hematogenic osteomyelitis; 2) osteomyelitis by contiguity, with or without vascular inadequacy; 3) vertebralosteomyelitis and 4) chronic osteomyelitis [5]. On the other hand, the Cierny-Mader's classification is focused on the portion of the affected and the physiological state of the host. Including local (chronic lymphedema venous stasis, retained foreign bodies, etc.) and systemic risk factors (tobacco abuse, immunedeficiencies, malnutrition, etc.) (2, 4, 5, 6, 7). Other researchers consider that the later classification has more evident clinical significance in treatment and prognosis of osteomyelitis, since it is more comprehensive, including consideration of other risk factors besides patient's bone injury (5). Regardless of model adopted, the distinct types of osteomyelitis require different clinical and surgical therapeutic strategies. The most common bone infections in decreasing order are: osteomyelitis secondary to contiguous-focus of infection or by direct inoculation (contamination after trauma or due to surgery); osteomyelitis due to vascular insufficiency and infection of surrounding soft tissue with the bone initially unaffected, including diabetic foot, andfinally, infections originating from the bloodstream in which the origin of infection is distant (5, 8). Bloodstream-sourced infections generally involve the metaphysis of long bones in children or vertebral bodies in adults (2, 9, 10). While the incidence of acute hematogenous osteomyelitis has been reducing in under 13-year-old children, bone infections by direct inoculation have increased over the last decades (11, 12). This is probably due to high-energy accidents and the growing use of orthopedic fixation devices and joint prosthesis (13). When gender are

compared, men present with higher rate of contiguous-focus osteomyelitis. In fact, men are more frequently involved in automobile accidents, which tend to cause exposed fractures with consequent high rates of infection (14, 15). This paper reviews the microbiologic, clinical and therapeutic considerations of osteomyelitis.

PATHOGENESIS

Microflora in Osteomyelitis

Staphylococcus Aureus remains the most common pathogen, but the percentage of, hematogenous osteomyelitis due to *S. aureus* has declined from 80 % to 90 % of cases to 40% to 605 in recent years (16-18).

Staphylococcus Epidermidis causes approximately 5% or fewer cases of disease. Because inadvertent contamination of cultures by the organism is frequent, its role as a pathogen in unknown**.**

Group A Streptococci isolates cause disease in children and occasionally in adults. **Group B Streptococci**. Are common in neonates and may be more common pathogen in this age group than are Staphylococci. Group B Streptococci also occur in diabetic patients (19).

Haemophilus Influenza is now an infrequent cause of osteomyelitis in the United States due to widespread usage of polysaccharide vaccine **Gram negative enteric bacilli** mostly *Escherichia coli, Salmonella* and Klebsiellaspecies, most often occur in adults and account for 10% to15% of cases of hematogenous osteomyelitis. Gram negative infections are common in certain predisposed hematogenous osteomyelitis e.g. Neonates (Enterobacteriacae),patients with sickle cell disease (*Salmonella*),and intravenous drug users(*Pseudomonas*).Patients with underlying chronic illness, including chronic renal disease, alcoholism,diabetes, andmalignancy, also have an increased risk of gram- negativeinfections. Anaerobes are uncommon cause of hematogenous osteomyelitis. Infections with multiple organisms (multiple infections) are not uncommon (20-23).

Mycobacterium Tuberculosis Tuberculous osteomyelitis should be suspected in any of vertebral osteomyelitis or osteomyelitis at any site that has not responded to antibiotic therapy. In the United States one-fifth of tuberculosis occur at extra pulmonary sites. One third of human immunodeficiency virus (HIV)-infected individuals with tuberculosis have extra pulmonary disease with or without pulmonary involvement (24).

Fungal Osteomyelitis Osteomyelitis can result from invasive infections due to a number of fungal pathogens, including *Candida*species.

Sporothrixschenckii, Coccidioidesimmitis, Blastomycesdermitidis, Histoplasmacapsulatum, Cryptococcusneo formans, and variety of less commonly encountered pathogens. Fungal osteomyelitis should be considered in any indolent osteomyelitis that has not responded to routine measures or in any patient with evidence of disseminated fungal disease. Therapy is generally complex and prolonged (25).

Diabetic Foot Infections The organisms isolated are related in part to the severity of underlying disease, which has been divided into mild non –limb threatening infections and more severe limb-threatening infections (26). Patients in both groups frequently receive multiple courses of different antibiotics. Recent receipt of antibiotics increases the likely hood of atypical or drug-resistant organisms, particularly MRSA, but also enterococcus and *Pseudomonas aeruginosa* (27, 28).

CLINICAL MANIFESTATION

There is lack of well-designed prospective clinical trials to guide the management of patients with osteomyelitis;

recommendations about management of this disease have been primarily derived from experimental animal models, expert opinion and retrospective cohort studies. Experimental models have been developed mainly to study the pathogenesis and treatment of osteomyelitis and to offer a more controlled approach to this heterogeneous *disease* (29).

Hematogenous Osteomyelitis

Acute Symptoms: The classic presentation of hematogenous osteomyelitis is sudden onset of bone pain and toxicity with high fevers, rigors, and diaphoresis.Most patients presents with symptoms of less than three weeks duration. Children and infants may be symptomatic for less than 1 week. Extensive use of antibiotics for conditions other than osteomyelitis may modify the clinical presentation. Atypical presentations are more common and uncommon sites more frequent ((16, 18, 30) Localized signs include limitations of the involved extremity, soft tissue swelling, erythema, warmth, and point tenderness over the involved area. Systematic manifestations are seen in 50% or fewer patients. They may include fevers, chills, nightsweats, anorexia, and weight loss. Minimal vague symptoms may be reported by as many as 40% of patients for 1 to 2 months. This indolent course is likely in the situations included: a) Primarysub-acute pyogenic osteomyelitis (Brodie abscess). This is characterized by the indolent formation of abscess, most frequently occurring at the metaphysis of long bones. Local pain is the most common presenting symptom (31). Vertebral osteomyelitis occurs more frequently in older patients and may result either hematogenous seeding of the bone or as the results of a postoperative wound infection and contiguous spread. Risk factors include diabetes, immunodeficiency, and intravenous drug users (32-34).c) Pelvic osteomyelitis the presenting symptoms for this condition may be unusual, including abdominal pain, gait disturbance, and sciatica (35).

Contiguous-Focus Osteomyelitis

Background Contiguous focus osteomyelitis due to spread from an adjacent focus of infection has some special characteristics. Postoperative infections constitute many cases of contiguous-focus osteomyelitis. Open reduction of closed fractures is the most common predisposing surgical procedure. Less common predisposing surgeries include craniotomies, prosthetic hip and other constructive joint surgery, tumor resections, and sternotomy for open heart surgery. These infections can be complicated by the use of foreign materials, includingmetal, plastic, and bone cement, which serve as a nisus of infection that is resistant to antibiotic therapy. Contamination of bone at the time of and open fracture is also common (36). Contiguous soft tissue infections, with spread to the bone, can involve any site: a) osteomyelitis also may occur by spread from an infected tooth socket, orsinuses, skin ulceration,wounds, or decubitus ulcers and from infections introduced by foreign bodies e.g. puncture wounds. b) Osteomyelitis frequently occur in bone underlying pressure ulcers and is particularly difficult to diagnose. Bone biopsy may be useful (37).

Clinical presentation Most patients follow an indolent course and are diagnosed within 1 to 2 months of the onset of disease. Delay in diagnosis often occurs in postoperative infections. This is related in part to the use of prophylactic or postoperative antibiotics, disease due to atypical organisms of low pathogenicity and the presence of foreign materials. Presenting symptoms include fever, regional soft tissue swelling, erythema and warmth. Purulent drainage from wounds and sinus tracts is common in both the acute and chronic forms. Site of involvement may affect the presentation. Osteomyelitis of cranial bones often lacks signs or symptoms of disease, whereas infection of long bones and pelvis often presents with fever pain (38).

Osteomyelitis Associated with Peripheral Vascular Disease

Background Most patients with osteomyelitis associated with peripheral vascular disease are diabetic. Osteomyelitis does occur however, in patients with severe atherosclerosis or vasculitis in the absence of diabetes.

Most patients are older than 50 years, and the bones of the toes and feet are most often involved. Neuropathy is present in most diabetic patients with foot disease predisposing to mechanical or thermal injuries. There is tissue ischemia such that ulcers occurring as result of trauma heal poorly, become chronic, and frequently extend into bone. Antibiotics penetrate poorly into these ischemic areas, frequently necessitating surgical debridement (39).

Clinical Presentation Few patients have systemic symptoms, and sepsis is rare. Local signs and symptoms predominate, including swelling and erythema. Pain may be absent in patients with advanced neuropathy. Osteomyelitis occurs from extension from cutaneous ulcers occurring over bony prominences. Osteomyelitis is more likely the more chronic deeper and wider ulcer.Crepitus of the soft tissues may be present due to either aerobic or anaerobic infection. Foul odor may be due to the presence of anaerobes or necrotic tissue (39, 40).Long standing diabetic complications are often the predominant findings. These include neuropathy, diminished or absent arterial pulses, skin and nail changes, retinopathy, and nephropathy. The presence of such complications may adversely affect disease outcome (39, 40)

Osteomyelitis Associated Diabetic Foot

Background Foot infections are a common cause of mortality and mortality in patients with diabetes. Twenty- five percent of all diabetics develop severe foot or leg problems. Foot infections account for 20% of diabetic hospitalization. At least 50% of all non-traumatic lower extremity amputations occurring in the United States are performed on diabetics (41). Peripheral neuropathy is likely the most important risk factor for development of foot lesions in diabetic patients. Neuropathy is present in over 80% of diabetic foot lesions (42). Loss of protective pain sensation due to peripheral neuropathy leads to loss of awareness of traumatic injury and subsequent breaks in the skin and skin ulceration (41).

Clinical Presentation Meaningful comparison of the many different studies on diabetic foot infections is hindered by lack of a uniform grading system accounting for neuropathy,ischemia, and wound depth, all thought to be a major predictors of poor outcome. Both the Wagner and University of Texas wound classification systems hold promise in this regard (43). Non-limb-threatening versus-limb threatening infections. Many researchers have suggested a practical clinical classification of infections that appear to be a useful approach In. Non-limb-threatening infections, patients have superficial infection and minimal cellulitis (<2cm of extension from portal of entry) and lack systemic toxicity. If an ulcer is present, it does not penetrate fully through the skin. These patients do not have bone or joint involvement or significant underlying ischemia In.limb-threatening infections, patients have more extensive cellulitis (>2cm of extension from portal of entry) and lymphadenitis. Full -thickness ulcers often are present. Infection of contiguous bones or joints occurs frequently. Significant ischemia with or without gangrene may be present. Fever is seen in only some patients and more common in those with extensive soft tissue involvement, deep plantar abscesses, bacteremia, or hematogenously seeded remote sites of infection (26).

Novel Osteomyelitis

Sapho (Synovitis, acne, pustulosis, hyperostosis and osteomyelitis) syndrome the cause of Sapho syndrome is unknown. Chronic recurrent multifocal osteomyelitis is the pediatric form of Sapho. First described in 1972, by Giedion and coworkers (44). The pathogenesis of the disease is unclear. More recent studies have implicated several genetic factors in the pathophysiology of the disease (45).Local swelling and tenderness of affected bonesare often present. Systemic symptoms of fever, weight loss, and generalized malaise are rare Osetitistypically is multifocal and affect several bones, including the chest wall bones (63%), pelvis (40%), and spine (33%) (46).Bone radiographs may show lytic erosions similar to those infectious osteomyelitis affecting the metaphysis. Cultures of biopsy material are negative for

bacteria, fungi and mycobacteria (47).

THERAPY

Most common pathogens in osteomyelitis in the descendingorder are: *Staphylococcus aureus, coagulase* negative *Staphylococcus, MRSA, Streptococci,and Enterococci,Enterobacteriaceae, Pseudomonas, mycobacteria*and a variety of fungi. In general the aim of therapy of osteomyelitis is to eradicate the infection and to restore function. Most cases of osteomyelitis in adults require a combination of medical and surgical therapy for successful eradication of the infection. It has long been realized that antimicrobial therapy alone is not curative in most cases of osteomyelitis. In 1941, withthe introduction of penicillin, Key wrote "continuous drug over a long period of time will lessen the amount of discharge, but it will not cure the disease because it cannot sterilize dead bone or cavities with necrotic content and rigid walls " (48).

β - Lactam and Vancomycin are the most commonly used antimicrobials in the medical management of osteomyelitis(49). Cephalosporin's and penicillinase-resistant penicillin are commonly used in patients with osteomyelitis because of their low toxicity profile and theirspectrum of activity against Staphylococci and other common bacterial pathogens that cause osteomyelitis. Cefazolin has excellent activity against methicillin sensitive Staphylococci, is safe, isinexpensive, and has been used extensively in the medical therapy of osteomyelitis (49). Ceftriaxone once daily is convenient for outpatient therapy; some experts advocate its use in methicillin-sensitive Staphylococcal osteomyelitis (49).

Vancomycin is used commonly in the treatment of osteomyelitis resulting from MRSA and ampicillin-resistant enterococci. Until more recently, it was the only available antimicrobial agent that was effective against these organisms despite its known lack of efficacy compared β-lactams when treating susceptible organisms. In a large cohort study of 450 patients with osteomyelitis who were followed for 10 years, vancomycin was associated with 2.5 relative risk of recurrence compared with a penicillinase-resistant penicillin in a univariateanalysis (50).Because of the high failure rate and the increasing minimal inhibitory concentration (MIC) among many *Staphylococcus*strains, many experts now advocate the use of higher and continuous dosages of vancomycin, keeping trough levels between 15- and 20µg/ml (50).

Linezolid is the first approved drug in the new oxazoliddinone class of antimicrobials. It has excellent activity against *Staphylococci, Streptococci,* and vancomycin- resistant *enterococci.* Linezolid has excellent bioavailability when administered orally. For all these characteristics, linezolid has been used in patients with infections resulting fromvancomycin-resistant enterococci or when β-lactams or vancomycin cannot be used (51). Prolonged used of linezolid has been associated with significant pancytopenia, peripheral neuropathy, and optic neuritis (52). Because of its toxicity profile, highcost, and experimental models showing a high failure rate, the use of linezolid in patients with osteomyelitis typically has been limited to patients with osteomyelitis resulting from vancomycin-resistant enterococci or patients who are intolerant to vancomycin (51, 53).

Daptomycin, a more recently approved cyclic lipopeptide antimicrobial agent, has bactericidal activity against aerobic and facultative gram-positive pathogens. The role of daptomycin in the treatment of patients with osteomyelitis was analyzed in 148 patients with osteomyelitis mostly caused by MRSA. After a short follow-up, 10% of patients failed therapy. The utility of daptomycin for the treatment of osteomyelitis caused by methicillin-susceptible *S. aureus* and vancomycin-resistant enterococci has yet to be defined (54).

The Optimal duration of antimicrobial therapy in osteomyelitis is unknown because of the lack of prospective randomized clinical trials assessing the length of antimicrobial therapy for patients with osteomyelitis and the heterogeneous nature of the disease. In experimental models, 4 weeks of therapy was more effective in sterilizing the bone than 2 weeks of therapy. Surgical debridement was not part of these models, however shorter courses of therapy may be

effective when extensive surgical debridement is accomplished (55). Many experts advocate a total duration of 4 to 6 weeks of parental antimicrobial therapy. When the surgical debridement of all infected bone is complete or the osteomyelitic bone has been resected, some experts advocate a short duration of antimicrobial therapy (56).

Hyperbaricoxygen therapy has been used as an adjunct measure for patients with chronic or refractoryosteomyelitis. It is hypothesized that an adequate oxygen tension is necessary for oxygen dependent killing of organisms by polymorph nuclear leucocytes and for fibroblast activity leading to angiogenesis and wound healing (57). The body of evidence suggests a favorable role in promotion of chronic ulcer healing and in the reduction of major limb amputation (58). But there is no randomized trails assessing the efficacy of hyperbaric oxygen therapy in humans with chronic or refractoryosteomyelitis, and its use in this scenario is still h8ghly controversial (57). The usual goal of therapy is the eradication of the infection and restoration of function. Treatment of chronic osteomyelitis usually requires aggressive surgical debridement and prolonged antimicrobial therapy (59).

CONCLUSIONS

Osteomyelitis is a common heterogeneous disease. Clinicians should be cautious that delay in diagnosis may result in high morbidity and mortality. Therefore familiarity with its, clinical sequelae along with therapeutic measures are essential for evidence based medicine. Pathological fracture is a devastating complication and eventually amputations with lifelong disability leading to deathare not uncommon. Most cases seem to have a favorable outcome with therapy resulting in eradication of infection and restoration of function.

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